THE MODERN LABORATORY INVESTIGATION OF A NEPHRITIC

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As a preliminary to the subject proper let me point out very briefly the present day conception of the rôle played by the kidney in the animal economy. Bayliss[1] in his recent work summarizes it as, first, the removal of non-volatile products of metabolism which are useless or injurious, and second, keeping the osmotic pressure of the blood constant. This osmotic pressure is due chiefly to the salts, and, their excretion must be increased or decreased according to the amount taken in with the food, and the excretion of water adjusted according to that taken in or lost in various ways.

For over seventy years two general theories of urinary secretion have existed—that of Ludwig on the one hand, and that of Bowman-Heidenhain on the other. According to Ludwig, secretion of urine is a process of simple filtration through the epithelium of the capillary wall and of the glomerular epithelium. With it are carried sodium chloride, other inorganic salts, and urea, and during its passage down the tubules concentration occurs by loss of water to the more concentrated blood and lymph.

On the other hand Bowman and Heidenhain held the glomerular process to be a secretory act, secreting water and inorganic salts, while urea and other urinary substances were secreted by the epithelium of the tubules.

Physiologists to-day are not agreed, but it is admitted that by whatever method, water and salts leave the kidney through the glomerulus and the majority incline toward the more active secretory method of Bowman-Heidenhain. Water is again resorbed by the urinary tubule epithelium and uric acid, phosphoric acid, and foreign substances are excreted here as well.

The functionating unit then of the kidney consists of a glom-

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erulus and the tubule which drains it into the kidney pelvis. Gerrish estimates that a normal kidney contains about half a million of such units and that the tubules would extend in total length about fifteen miles.

Just as the normal heart has a great reserve of power, so the kidney possesses a great reserve of function. Indeed it has been estimated that one half of one kidney or one fourth of the total kidney substance is quite able to carry on the necessary excretion. Herein lies the explanation of the fact that a person may live with a large portion of the kidney substance diseased. Under such circumstances, however, the healthy parts functionate under increased tension and must have a perfect blood supply. Any interference with this supply, either local or general, proves immediately serious. Similarly any poison or irritant substance provides a serious menace to such a case.

The blood supply of the kidneys is large. Councilman[2] estimates that this supply may vary nineteen times as much as the average supply to other organs.

The volume of urine eliminated varies with many factors, but chiefly with the fluid ingested and the condition of the circulation. If the blood is hydræmic from ingestion or from the elimination of exudates and œdemas, this favours the condition of polyuria. Rises of blood pressure tend in a general way to increase the amount excreted and *vice versa*. Of course, here it must be remembered that the rise in blood pressure may be offset by a constriction of the renal vessels. Drugs of the caffeine group produce diuresis largely by the improvement of the circulation through the kidney and partly by direct stimulation of the renal cells. Digitalis, in addition to helping the circulation dilates the renal vessels and according to some observers has a specific action upon the kidney cells.

Having thus briefly referred to this aspect of kidney physiology, let me refer back to what is designated as the kidneys first function, i.e., the removal of the non-volatile waste products of metabolism. Since protein substances are essential constituents of all living cells, and without them vegetable as well as animal life is impossible, it necessarily follows that we cannot adequately consider disturbances of kidney function without at least some familiarity with the more outstanding phases of the metabolic processes which concern these substances.

Proteins differ from fats and carbohydrates by containing nitrogen in addition to the carbon, hydrogen, and oxygen common

to all. Generally sulphur and sometimes phosphorus are constituents. The most important element, however, is nitrogen.

Decomposition or cleavage of protein substances is brought about by hydrolysis, and this occurs in digestion by the action of the proteolytic enzymes. In this process the protein molecule is gradually broken down and less complicated aggregates first result which are known as proteoses, peptones, and peptides, and these still possess true protein characteristics. Further hydrolysis results in the transformation of these simpler protein substances into amino acids of a known chemical structure, and devoid of any protein characters. Thus from protein, of huge molecule, colloid, slightly soluble, and non-diffusible, we pass by way of proteoses, peptones, and peptides to a class of simpler crystalline substances which are for the most part readily soluble and diffusible. I shall not here enumerate the long list of these amino acids which is contained in any reference book.[3] Suffice it to say that they are most important, and are amphoteric, being able to form salts with both bases and acids.

Some of these amino acids are destroyed by intestinal bacteriæ but most of them reach the portal blood, thence through the liver to the systemic circulation where some of them are eagerly seized by the tissue cells and synthesized into the various complex proteins of the organism. Others remain in the blood and there is always a certain equilibrium between the amino acid content of tissues and blood.

In the process of tissue building the great diversity of amino acids required for different tissues leads to the rejection of some, which if not specifically required, are carried to the liver where the nitrogenous portion is converted to urea. In addition it is believed that there is a constant migration of amino acids from tissue due to disintegration of tissue proteins. Some of these are likewise in the liver converted to urea.

This conversion from amino acids to urea is carried out by:

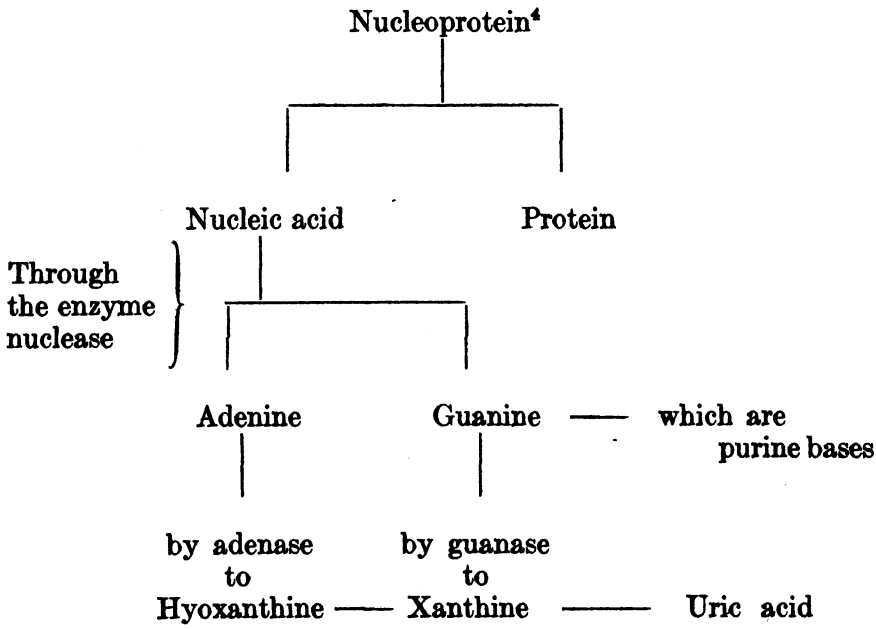
1. Deaminization, or the splitting off of ammonia.
2. This ammonia unites with CO_2 of the blood to form ammonium carbonate.
3. Which in turn is converted to ammonium carbonate,
4. And finally to urea, which is the principal end product of ordinary protein metabolism in human beings.

It is believed that other tissues of the organism besides the liver have very slight power of urea formation.

A second very important decomposition product of protein

metabolism is ammonia, which may be liberated in the intestines during digestion and thence pass to the liver where it may be converted to urea. Some of this ammonia as well as ammonia from deaminization may escape transformation into urea, in order that when excreted by the kidney later it may neutralize the sulphuric, phosphoric, and uric acids of the urine.

A third product of protein cleavage is uric acid which arises from the breaking up of nuclear material. This process may be exogenous, in the intestines due to trypsin, or endogenous in the tissues due to a similar enzyme. Foods such as pancreas, thymus, liver, kidney, and testicles are rich in nucleoproteid.



A small amount escapes conversion into uric acid and gives rise to the purine bases of the urine.

The substitution[5] of uric acid for urea as the form of nitrogenous waste in reptiles and birds is an adaptation to conserve the water of the body and fit them for a dry climate. Uric acid has very little affinity for water and is almost insoluble, and in birds urine is excreted as crystalline masses, while urea has a great affinity for water and takes a great deal of water out of the body with it while being excreted. In birds, however, the formation of uric acid is analogous to the formation of urea in man, i.e., by

a synthesis chiefly in the liver. In man, it is worthy of note, that a small part of the ingested purines are converted into uric acid later, and the remainder probably are destroyed by bacteria in the intestine or in the tissues.

Creatinine is a substance found in the blood and excreted in the human urine in amounts of 1 to 2 grams daily and is entirely independent of the protein intake. The amount is roughly proportional to the body weight—about 7–11 mgs. of creatinine nitrogen per kilo of body weight. This is termed the creatinine cœfficient.[6] It is found normally in the liver, heart, and voluntary muscle as well as in the brain, testicles, and some other organs. The antecedent state of creatinine is creatine and the muscles and some other organs including the kidney likely have the capacity of converting creatine into creatinine. Folin suggests, in view of all the known facts in reference to creatinine, that it is entirely endogenous in orgin and that it is an index of the real catabolism of the vital machinery of the body proper, in distinction from that catabolism which increases the free energy.

These then are the most important non-volatile products of metabolism which it is incumbent upon the kidney to remove, and even this brief and incomplete resumé of their origin and place in the economy of the organism may help to make clear some of the problems in dealing with our nephritics.

Turning now to the methods of attack in dealing with this subject, they naturally divide themselves into two groups: first, we may determine to what extent the kidney eliminates normal substances and also foreign substances such as drugs or dyes; and secondly, we may determine if any degree of retention of certain substances exists in the blood. The broad underlying principle of all tests then is that any depreciation of renal activity will be reflected in the urine on the one hand, and in the blood upon the other.

Let us first consider the examination of urine.

The elimination of water. The healthy kidney possesses to a marked degree the capacity of being able to adapt itself to any tendencies which are likely to alter the molecular concentration of the blood, e.g., the adding or subtracting of water from the blood. Normally water in excess is quickly eliminated by the glomerules and reabsorption in the tubules is inhibited, for, as you know, the glomerulus normally secrets a urine of low specific gravity, and the tubule absorbs water and some salts back into the blood again, thus concentrating it. If, on the other hand, the

supply of water to the body is limited, the absorptive capacity of the tubules is given full play, resulting in a urine of high specific gravity and saving considerable water to the organism. This is the diluting-concentrating power of the kidney and obviously suffers in disease of the kidney in proportion to the amount of parenchyma involved. A normal kidney, by adapting itself to changing influences, gives a very varied secretion, while a diseased one tends more to constancy and invariability.

In order to test this capacity in the kidney a provocative polyuria[7] test is used. The patient empties the bladder say, at 7.30 a.m. and drinks one pint of water, on an empty stomach, and remains in bed during the test. Then collect urine at 8.30, 9.30, 10.30, and 11.30 and note the amount and specific gravity of each. In three hours the patient should have passed at least one pint of urine. Under normal circumstances the polyuria appears in the first half hour, and reaches its maximum soon after.

To render this test more comprehensive, Hedinger and Schlayer[8] have proposed a test to determine the water, salt, and specific gravity of two-hourly specimens. Their work shows how normal and diseased kidneys respond to a reasonable amount of fluids, salt and purine. More recently Mosenthal,[9] in an admirable paper covering a study of one hundred cases, elaborates upon their method and his findings and conclusions are exceedingly instructive. I here quote freely from his article and many of these charts are from the same source. His test meal for renal function as used at John's Hopkins Hospital is here given.

NEPHRITIC TEST DIET

For..... Date.....

All food is to be salt-free from the diet kitchen.

Salt for each meal will be furnished in weighed amounts (213 gm.)

All food or fluid or salt not taken must be weighed or measured after meals and chartered in the spaces below;

Allow no food or fluid of any kind except at meal times.

Note any mishaps or irregularities that occur in giving the diet or collecting the specimens.

Breakfast, 8 a.m.:

Boiled oatmeal, 100 gms.
Sugar, 1 to 2 teaspoonfuls.
Milk, 30 c.c.
Two slices of bread (30 gms. each).
Butter, 20 gms.
Coffee, 160 c.c.
Sugar, 1 teaspoonful } 200 c.c.
Milk, 40 c.c.

Milk 200 c.c.
Water, 200 c.c.

Dinner, 12 Noon:

Meat soup, 180 c.c.
Beefsteak, 100 gms.
Potato (baked, mashed or boiled), 130 gms.
Green vegetables as desired.
Two slices of bread (30 gms. each).
Butter, 20 gms.
Tea, 180 c.c.
Sugar, 1 teaspoonful } 200 c.c.
Milk, 20 c.c.
Water, 250 c.c.
Pudding (tapioca or rice), 110 gms.

Supper, 5 p.m.:

Two eggs cooked in any style.
Two slices of bread (30 gms. each).
Butter, 20 gms.
Tea, 180 c.c.
Sugar, 1 teaspoonful } 200 c.c.
Milk, 20 c.c.
Fruit (stewed or fresh), 1 portion.
Water, 300 c.c.

8 a.m. No food or fluid is to be given during the night or until 8 o'clock the next morning (after voiding), when the regular diet is resumed. Patient is to empty bladder at 8 a.m., and at the end of each period, as indicated below. The specimens are to be collected for the following periods in properly labelled bottles, to be furnished by the chemical division of the medical clinic:

8 a.m. to 12 n.; 12 n. to 2 p.m.; 2 p.m. to 4 p.m.; 4 p.m. to 6 p.m.; 6 p.m. to 8 p.m.; 8 p.m. to 8 a.m.

Specimens are to be left in the ward until called for at 8.30 a.m. by an attendant from the chemical laboratory.

The above dietary contains 13·4 gm. N., 8·5 gm. NaCl. and 1760 c.c. of fluid and considerable purin material in meat, soup, tea, and coffee. It is in no way a specific one but merely such as may be supplied in almost any home and contains a sufficient quantity of diuretic material to make an adequate demand on the kidney to test renal function.

Patients are requested to take no solid food or fluid between meals or during the night, and each two-hour specimen is collected promptly, and the night urine secured ere breakfast is eaten.

If patients are irrational, or involuntary, piecemeal studies alone are possible, but such, repeated as occasion offers, supply much valuable data.

In a normal individual the points noted below are the important ones to observe in the response to a nephritic test meal:

1. Variations in the specific gravity of the urine—usually an average of at least ten points.

2. Balance between intake and output of salt, nitrogen, and fluids—should be approximately equal.

3. Night urine—should be of high specific gravity (above 1016), high in percentage of nitrogen (above 1 per cent.), and small in amount (400 c.c. or less) regardless of fluid ingested. This is the concentration power of the kidney.

NORMAL RESPONSE TO NEPHRITIC TEST MEAL

Time of day.	Amt.	Spec. Grav.	NaCl per cent.	Grams	Nitrogen per cent.	Grams.
8—10 a.m.....	153 c.c.	1016				
10—12 "	156 "	1019				
12— 2 p.m.....	194 "	1012				
2— 4 "	260 "	1014				
4— 6 "	114 "	1020				
6— 8 "	238 "	1010				
Total day.....	1115	....	....	9·36	....	7·32
Night 8—8.....	375	1020	....	2·36	1·23	4·61
Total 24 hours...	1490	....	....	11·72	....	11·93
Intake.....	1760	....	....	8·5	....	13·4
Balance.....+270		....	....	−3·22	....	+1·47

In disease conditions the kidney shows its dimished capacity by:

1. Fixation of concentration—or hyposthenuria, of Koranyi.

2. Some retention of one, two, or three of the following—sodium chloride, nitrogen, or water.

3. The night urine shows polyuria—an amount over 400 c.c. and not merely frequency of micturition. This is often the earliest symptom of renal disease. Lower specific gravity and lower nitrogen concentration are also frequently met. Normally, after nitrogen intake, its appearance in the urine is somewhat delayed, giving rise to disproportionately high nitrogen content in night urines over that of the day, commonly above 1 per cent.

Diseased conditions giving rise to variations from the normal findings, in addition to the nephritides, are œdema due to cardiac decompensation, severe anæmia, diabetes insipidus, conditions of back pressure on the kidney, as in hydro-nephrosis, hypertrophied prostate, and other kidney conditions such as the ascending infections.

SPECIFIC GRAVITY OF URINES COLLECTED IN TWO-HOURLY PERIODS

Case	Specific Gravity						Variation in Degrees
Normal	16	19	12	14	20	10	10
Incipient primary contracted kidney	09	14	09	10	14	06	8
Incipient primary contracted kidney	18	09	16	22	13	10	11
Advancing primary contracted kidney	18	17	13	13	13	15	5
Advancing primary contracted kidney	19	20	20	20	21	20	2
Advanced primary contracted kidney	11	11	10	11	11	11	1
Advanced primary contracted kidney	12	11	11	11	12	13	2
Advanced primary contracted kidney	10	09	10	09	09	10	1
Advanced primary contracted kidney	05	06	07	08	..	08	3
Incipient chronic diffuse nephritis	25	..	24	33	28	30	9
Incipient chronic diffuse nephritis	09	16	15	17	12	07	10
Advanced chronic diffuse nephritis	12	11	14	11	13	11	3
Secondary contracted kidney	09	10	12	10	12	10	3
Myocardial decompensation—congestion	18	20	19	18	20	21	3
Mycocardial decompensation—congestion	25	24	24	25	24	21	4
Myocardial decompensation—congestion	12	15	10	15	13	10	5
Polycystic kidney	10	10	10	11	10	10	1
Marked anæmia	10	10	10	10	10	11	1
Diabetes insipidus	04	04	06	04	04	04	2
Cystitis, pyelitis, prostate hypertrophy	10	10	10	10	11	11	1
Pyonephrosis	11	12	12	12	13	12	2

These are day urines. Noted fixed specific gravities.

CHART SHOWING (1) FIXED SPECIFIC GRAVITY, AND (2) CONSTANCY OF NOCTURNAL POLYURIA, IN A CASE OF ADVANCED CHRONIC DIFFUSE NEPHRITIS

Volume of Urine c.c.		Specific Gravity		Volume of Urine c.c.		Specific Gravity	
Day	Night	Day	Night	Day	Night	Day	Night
1390	560	12	10	1525	1090	12	11
935	710	12	11	1400	1260	11	10
1010	760	11	10	1146	1100	11	12
1122	705	10	10	1940	1060	10	09
790	790	10	10	1280	1520	10	09
908	1110	11	10	1640	1400	10	10
880	1184	11	10	1370	1370	11	10
1020	1360	12	09	1480	1480	18	18
1075	1120	11	10	1340	1680	19	17
1140	1255	10	10	1410	1340	10	10
1375	730	12	11	1480	1410	12	10
1600	1160	12	10	1184	1610	10	08

CHRONIC INTERSTITIAL NEPHRITIS

In early nephritis variations in renal function do not necessarily parallel the anatomical changes or *vice versa*, owing to the great reserve of kidney structure. If there is a large percentage of kidney tissue diseased or destroyed the remainder must obviously func-

tionate nearly up to, or quite up to, its full capacity, constantly, and hence little or no variations are possible in spite of varying demands. This gives rise to urines from hour to hour or even day to day of almost fixed characteristics, i.e., as to specific gravity, salt, and nitrogen.

Different stages are of course met, from slight nocturnal polyuria (more than 400 c.c.) with milder degrees of retention of salt and nitrogen, through various phases to the most severe cases.

These are summarized by Mosenthal as follows:

1. Nocturnal polyuria (over 400 c.c.).

2. Tendency to total polyuria (volume of urine equals or surpasses the volume of ingested fluids).

3. Fixation of specific gravity—gradually becoming more intense. Fixation at first occurs at higher levels and later at lower.

4. Fixation of two-hourly quantities, i.e., the usual polyuric response to meals is absent.

5. Night urine may drop to normal quantity but is of low specific gravity and nitrogen content.

6. Varying degrees of nitrogen and salt retention.

The accompanying tables indicate graphically the points enumerated.

EARLY HYPERTENSIVE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	465	1·009				
10—12	102	1·014				
12—12	205	1·009				
2—4	160	1·010				
4—6	116	1·014				
6—8	160	1·006				
Total Day	1,208			4·79		5·67
Night 8—8	935	1·010	0·33	3·08	0·50	4·67
Total 24 hours	2,143			7·87		10·34
Intake	1,760			7·50		13·40
Balance	−383			−0·37		+3·06

The nephritic test meal shows a tendency toward fixation of specific gravity and a distinct nocturnal polyuria in an early case of hypertensive nephritis.

REACTION TO NEPHRITIC TEST MEAL IN ADVANCED HYPERTENSIVE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm
8—10	133	1·010				
10—12	176	1·009				
12— 2	156	1·010				
2— 4	212	1·009				
4— 6	164	1·009				
6— 8	104	1·010				
Total Day	945		0·34	3·33		3·27
Night 8—8	590	1·010		2·01	0·38	2·24
Total 24 hours	1,535			5·34		5·51
Intake	1,510			5·80		2·20
Balance	−25			+0·46		+6·69

There is very marked fixation of the percentage figures for nitrogen and salt concentration and the specific gravity. There is evident nitrogen retention. The salt intake is too low to make it certain that a diminished ability to excrete salt does not exist.

EXTREME INTERSTITIAL NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	24	1·005				
10—12	106	1·006				
12— 2	82	1·007				
2— 4	83	1·008				
4— 6	0					
6— 8	230	1·008				
Total Day	525		0·12	0·63	0·25	1·28
Night 6—8	1,140	1·007	0·12	1·37	0·20	2·27
Total 24 hours	1,665			2·00		3·55
Intake	1,850			6·00		13·00
Balance	+185			+4·00		+9·45

Note the low fixed specific gravity, the retention of salt and nitrogen, and the night urine which is increased in amount, shows a low specific gravity and a low nitrogen concentration.

RENAL CONGESTION, FROM MYOCARDIAL INSUFFICIENCY

These cases give the following characteristics due to the congestion and œdema affecting the kidney function:

1. Specific gravity fairly constant at a point about 1020.
2. Very low salt output.
3. Markedly good output of nitrogen—in contrast to that of salt.

4. An oliguria.
5. A normal night urine.

It is thus of considerable value to use a nephritic test meal to estimate roughly the degree of cardiac decompensation since the kidney is so sensitive to circulatory disturbances.

The following charts illustrate a couple of marked cases.

URINE IN MARKED CARDIAC DECOMPENSATION

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	65	1·025				
10—12	53	1·024				
12— 2	51	1·024				
2— 4	49	1·025				
4— 6	37	1·024				
6— 8	57	1·021				
Total Day	312		0·58	1·81	1·53	4·77
Night 8—8	172	1·021	0·42	0·72	1·67	2·87
Total 24 hours	484			2·53		7·64
Intake	995			7·00		9·40
Balance	+511			+4·47		+1·76

Test meal in an individual with marked cardiac decompensation which has persisted for some time.

URINE IN EXTREME CARDIAC DECOMPENSATION

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	61	1·018				
10—12	52	1·020				
12— 2	65	1·019				
2— 4	55	1·018				
4— 6	30	1·020				
6— 8	35	1·021				
Total Day	298			0·77		5·01
Night 8—8	275	1·021	0·31	0·85	1·85	5·07
Total 24 hours	573			1·62		10·08
Intake	570			5·00		12·00
Balance	−3			+3·38		+1·92

Note the high concentration of nitrogen as compared with the low figures for salt. There is a distinct oliguria. (The water output should be higher as general anasarca was present.)

In a combination of cardiac insufficiency and interstitial nephritis the urinary symptoms of either may predominate. The determining factor which decides the symptom type is probably whether or not the nephritis is so far advanced as to present an unchanging barrier to the influence of renal congestion.

Chronic Diffuse Nephritis

Here the response to the functional tests vary as much as do the clinical symptoms. During œdema formation there is salt and water retention, nocturnal polyuria with good nitrogen excretion. Hence the urinary output is very like that of cardiac decompensation. While œdema is being eliminated salt and water are above the intake and night polyuria is marked.

Chronic Diffuse Nephritis

	Urine		Sodium Chlorid		Nitrogen	
Time of Day	c.c.	Sp. Gr.	Per cent.	Gm.	Per cent.	Gm.
8—10	32	1·025				
10—12						
12— 2	54	1·024				
2— 4	64	1·033				
4— 6	64	1·028				
6— 8	66	1·030				
Total Day	280			0·50	1·91	5·34
Night 8—8	595	1·016		0·46	0·93	5·53
Total 24 hours	875			0·98		10·87
Intake	1,760			8·50		13·40
Balance	+885			+7·52		+2·53

Test meal in a case of chronic diffuse nephritis during the formation of œdema. The marked salt and walter retention, the night poyyuria and the high nitrogen excretion are characteristic.

Chronic Diffuse Nephritis

	Urine		Sodium Chlorid		Nitrogen	
Time of Day	c.c.	Sp. Gr.	Per cent.	Gm.	Per cent.	Gm.
8—10	230	1·022				
10—12	130	1·025				
12—2	118	1·022				
2— 4	136	1·022				
4— 6	96	1·020				
6— 8	108	1·014				
Total Day	818			8·24		9·71
Night 8—8	950	1·014		7·61	0·73	7·14
Total 24 hours	1,768			15·85		16·85
Intake	1,760			8·50		13·40
Balance	−8			−7·35		−3·45

The results of a test meal during the stage of elimination of œdema. Note the large amount of fluid, salt, and nitrogen excreted.

CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	328	1·012				
10—12	174	1·011				
12— 2	248	1·014				
2— 4	279	1·101				
4— 6	88	1·013				
6— 8	100	1·011				
Total Day	1,217			4·08		9·88
Night 8—8	490	1·014		1·66	1·01	4·95
Total 24 hours	1,707			5·74		14·83
Intake	1,860			8·50		10·30
Balance	+153			+2·76		-4·53

The marked involvement of renal function is evident from the low fixed specific gravity.

THE SAME CASE ONE MONTH LATER

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid Per cent.	Sodium Chlorid Gm.	Nitrogen Per cent.	Nitrogen Gm.
8—10	216	1·009				
10—12	75	1·016				
12— 2	156	1·015				
2— 4	124	1·017				
4— 6	186	1·012				
6— 8	380	1·007				
Total Day	1,137			3·41		6·82
Night 8—8	400	1·007		1·52	1·17	4·68
Total 24 hours	1,537			4·92		11·50
Intake	1,760			6·20		13·40
Balance	+223			+1·27		+1·90

The marked clinical improvement is reflected in the result which closely approaches the normal.

To sum up then, involvement of the kidney function is first evidenced by changes in the night urine:

1. Increase in the amount—nocturnal polyuria.
2. Lowering of specific gravity.
3. Lowering in the percentage of nitrogen.

One or all of these phenomena may be present.

In severe cases marked functional impairment is indicated by:

1. Fixed and low specific gravity of day urine.

2. A diminished output of salt and nitrogen.
3. Tendency to a total polyuria.
4. Night urine of (a) Increased volume.
   (b) Low specific gravity.
   (c) Low nitrogen content.

In diffuse or parenchymatous nephritis the picture is a variable one—but gives much helpful information, as it does also in cardiac decompensation.

Were kidney entirely uninfluenced by extrarenal factors, the examination of the urine for urea and total nitrogen would be much more conclusive than it is, as an estimate of renal function. The data so derived gives general information of very positive value indeed, but is not to be interpreted as necessarily a quantitative estimate of renal damage.

Before leaving the subject of the urine one must refer to the test introduced by Rowntree and Geraghty[10] in 1910—phenolsulphonephthalein. It is an excellent test, easily carried out and simply read if one possesses even a very primitive form of colorimeter. Its use is based upon the knowledge that a definite amount of the dye is excreted in two hours in health, while with disturbance of function marked delay occurs in its elimination. In health 60 per cent. is eliminated in two hours. Suffice it to say that since its introduction it has received world-wide recognition and is to-day looked upon as an exceedingly valuable test, for both diagnosis and prognosis.

It is especially useful in surgical procedures on the kidney—where the comparative function of each kidney is of great importance.

Let us then turn to the other method of attack in studying renal disorder, and that is to see what degree of retention, if any, is present, in the blood, of those substances which the kidney normally excretes in adequate amount. At an earlier part of my remarks I referred to the end products of protein metabolism with which of course the kidney is very specially concerned, since one of its chief functions is the elimination of such waste products. They are grouped together under the name of non-protein, or incoagulable nitrogen, and in this term are included urea, ammonia, uric acid, creatinine, creatin, and an undetermined fraction which includes amino-acid nitrogen, and may be termed residual nitrogen.

The accompanying chart indicates their percentages of the total non-protein nitrogen in both blood and urine.

THE COMPARATIVE NITROGEN PARTITION OF URINE AND BLOOD IN PER CENT. OF TOTAL NON-PROTEIN NITROGEN AS INDICATED BY MYERS AND LOUGH[11]

Fluid.	Urea N.	Uric Acid N.	Creatinine N.	Creatin N.	Residual N.
Normal Urine	85	2	5	4	4
Normal Blood	50	3	2	0·3	46
Uræmic Blood	75	2·4	2·5	0·5	20
Nephritic	55	2·2	2	0·3	41
Gouty	50	6·0	2	0·3	42

These figures refer purely to the component parts going to make up the non-protein nitrogen and not at all to the amount of retention.

Progress along these lines of investigation is due largely to the work of Professor Folin[12] and his co-workers, also Frothingham,[13] Fitz,[14] Myers and Fine,[15] Benedict,[16] Foster,[17] Marshall,[18] and several other laboratory workers.

Normally these substances are found in the blood in a certain concentration, and if the kidney excretory power is markedly impaired it obviously follows that it will have difficulty in eliminating these very substances, upon the elimination of which it ordinarily expends so much of its energy, and that hence their concentration in the blood will increase.

Considering the most comprehensive first, non-protein nitrogen, Obermayer and Popper[19] first called attention to its increase in the blood in uræmic states. The normal amount in the blood is estimated as 25 to 30 mgms. per 100 c.c. although Gettler and Baker assign it an upper level of 45 mgms. In various kidney disabilities this may rise to over 350 mgms per 100 c.c. Frothingham and Smillie[13] have shown a very definite parallelism between the results of this and the phenolsulphonephthalein tests on the same cases.

Tileston and Comfort[20] in a very comprehensive study of one hundred and forty-two cases of considerable variety summarize as follows:

1. Fasting adults showed 22·9 to 25 mg. non-protein nitrogen per 100 c.c. of blood, and the urea nitrogen was 12 to 14 mg. per 100 c.c. of blood.

2. After full meals with meat there was a rise of 4·7 mg. of non-protein nitrogen and 2·5 mg. of urea nitrogen.

3. Cases of chronic nephritis, both interstitial and diffuse, without uræmia, showed moderate elevations, or were normal, while uræmic cases were all elevated.

4. Phenolphthalein tests were roughly proportional to the degree of retention, although some cases with good phthaleins showed retention.

5. Patients with over 100 mg. usually die within four or five weeks.

6. Nephritics with retention should have a restriction of protein which reduces the amount of retention.

7. In chronic passive congestion there is no retention of nitrogenous waste.

8. A marked elevation of N.P.N. makes a patient a poor operative risk.

9. Eclampsia seldom shows marked retention of N.P.N. and hence differs from true uræmia.

10. Compensated valvular disease, acute pericarditis, acute endocarditis, malignancy, typhoid, scarlet fever (uncomplicated), and acute rheumatism all gave normal values.

11. Thirty-six per cent. of all syphilitics examined, in various stages, showed a considerable degree of retention.

We may next turn to the urea of the blood, whose estimation has been rendered practical by Marshall with the urease prepared from the soy bean, which breaks up the urea and enables its estimation as ammonia. By reference to the table you will note the very large place which the urea occupies in the total non-protein nitrogen of the blood. Tileston and Comfort found it to be about 50 per cent. of the total N.P.N. in normal cases but in cases of marked retention the urea usually formed about 70 per cent. of it. They conclude that the determination of the total N.P.N. is of more value than the determination of the urea alone. Normal values for urea in the blood vary from 12 to 15 mgms. per 100 c.c.

The elimination of uric acid and its presence in the blood forms a very interesting chapter in pathological chemistry. In 1848, Sir A. B. Garrod[21] drew very interesting conclusions which are in surprising harmony with the views of to-day, especially when we consider the methods at his disposal. Until recently, no special advance has been made in the solution of this problem, and this advance is due to Folin's work and methods. Retention of uric acid even in large amounts, as evidences by recent methods of examination, does not necessarily lead to gout, but as Von Noorden[22] says, in addition to its retention there must be the accession of another unknown factor, before the deposition of uric acid occurs.

Uric acid is excreted by the kidney with greater difficulty than

is the case with other nitrogenous waste products, urea, and creatinine. Creatinine is excreted most easily, then urea and then uric acid. This fact is evidenced by the appended chart of Chace and Myers[23] which shows graphically the "staircase" effect produced by these phenomena. High uric acid content of the blood was frequently noted without retention of any other waste products.

Diagnosis	Condition	Mgms per 100 c.c. of blood			Phthalein 2 hrs. %	Syst. B.P.	Urine Alb.	Urine Casts
		Uric Acid	Urea N.	Creatinine N.				
Pulmonary tuberculosis. . .	Unchanged	6·5	16	2·7	58	130	++	+
Pericarditis.	"	5·6	13	2·1	45	150	-	-
Interstitial nephritis.	"	5·5	12	2·5	37	185	-	+
Diffuse nepritis.	"	9·6	19	2·4	45	175	+	+
Early interstitial nephritis..	"	9·5	25	2·5	13	185	+	+
Early interstitial nepritis....	"	6·6	24	3·3	26	185	-	+
Early interstitial nephirits..	"	8·7	20	3·6	20	100	+	+
Early interstitial nephritis..	"	6·3	31	2·0	23	150	-	-
Moderately severe chronic interstitial nephritis.	Improved	8·0	80	4·8	0	240	++	++
		4·9	17	2·9	10	170		
Moderately severe chronic diffuse nephritis.	Improved	8·3	72	3·2	25	238	+++	++
		5·3	21	1·9	43	145		
Moderately severe chronic diffuse nephritis.	Improved	9·5	44	3·5	38	210	++	++
		2·5	19	1·9	52	120		
Typical fatal case of chronic interstitial nephritis.	Died	22·4	236	16·7	0	210	++	pus
Typical fatal case of chronic interstitial nephritis.	"	15·0	240	20·5	2—3	225	++	+
Typical fatal case of chronic interstitial nephritis	"	14·3	263	22·2	0	220	++	+
Typical fatal case of chronic interstitial nephritis.	"	8·7	144	11·0	trace	225	+	+
Normal—uric acid		2—3 mg						
urea		12—15 "						
creatinine		1—2.5"						

per 100 c.c.

Since uric acid is eliminated with most difficulty, it follows, that its retention would likely be among the first evidences of disturbed function. The normal content of the blood is 2 to 3 mgms of uric acid per 100 c.c. of blood.

According to the above statements then, we would infer that

the retention of creatinine in the blood signified marked impairment of kidney function, since as Folin and Denis remark it is "removed by the human kidney with an ease and certainty, exceeded only by the facility of removal of the ammonium salts." Since it is so easily removed normally, its retention must mean very marked impairment of renal function. As already observed, creatinine on a meat free diet is entirely endogenous in origin and its formation is very constant. Hence a lowered nitrogen intake lowers the concentration of urea and uric acid, but does not influence that of creatinine. All cases, followed by Myers, with 5 mgms or over per 100 c.c. of blood have died. Normal values are 1 to 2·5 mgm. per 100 c.c. of blood.

URIC ACID IN THE BLOOD IN CASES OF INCIPIENT INTERSTITIAL NEPHRITIS.[22]

Diagnosis	Mg. to 100 c.c. blood			Phthalein 2 hrs.	B.P.		Urine	
	Uric Acid	Urea Nitrogen	Creatinine		Syst.	Diast.	Alb.	Casts
Interstitial nephritis.....	9·5	25	2·5	13	185	90	+	+
Fibrillation.....	9·3	14	2·9	44	120	90	-	-
Cirrhosis, nephritis, alcoholism..	8·7	20	3·6	20	100	87	+	+
General œdema	7·7	20	2·6	45	168	100	+	-
Carcinoma of stomach	7·5	16	2·2	50	150	90	-	-
Interstitial nephritis.....	7·1	16	2·0	26	185	110	-	+
Carcinoma of stomach	6·8	20	1·8	40	140	80	-	+
Pulmonary and kidney Tuberc .	6·5	16	2·7	58	130	90	++	+
Hypothyroidism and nephritis .	6·3	31	2·0	45	150	90	-	-
Syphilis and nephritis.....	6·3	17	2·7	38	185	80	++	+
Chronic arthritis and nephritis..	6·1	12	2·4	65	145	80	+	+
Pericarditis, alcoholism.....	5·6	13	2·1	45	150	65	-	-

Myers considers blood creatinine a much better prognostic guide than phthalein estimations, since the creatinine continues to show marked variations after the phthalein results are continuously negative, and hence variations in the patient's condition may still be taken cognizance of thus.

PROGNOSTIC VALUE OF CREATININE IN THE BLOOD OF NEPHRITIS.[23]

Cases	Blood Creatinine	Phthalein 2 hrs.	Termination
1	33·3	....	Died
2	28·6	0	"
3	22·2	0	"
4	20·5	2–3	"
5	20·0	0	"
6	20·0	0	"
7	18.9	0	"

PROGNOSTIC VALUE OF CREATININE IN THE BLOOD OF NEPHRITIS—*Continued*

Cases	Blood Creatinine	Phthalein 2 hrs.	Termination
8	17·8	....	Died
9	16·7	0	"
10	16·6	Trace	"
11	14·7	....	"
12	14·7	0	"
13	14·3	0	"
14	12·7	1	"
15	12·5	0	Stationary
16	11·1	3	Died
17	11·1	0	"
18	11·0	3 to 1	"
19	10·7	0–5–4–3–6	"
20	10·0	0	"
21	9·0	0	"
22	8·3	6–4–2	"
23	7·4	0	"
24	7·0	0	"
25	6·7	5	"
26	6·1	9	"
27	5·9	3	"
28	5·6	2–7–10	Improved
29	5·5	....	Died
30	5·4	13–4	Stationary
31	5·3	10	Died
32	5·2	....	"
33	4·9	....	"
34	4·8	0–10–31	Stationary

I should not conclude this part of my remarks without referring briefly to another method of estimation of the kidney function. I refer to Ambard's coefficient of urea excretion.[24] Ambard demonstrated that normally a constant relationship exists between the concentration of urea in the blood and the amount of urea excreted in a given portion of time, i.e., the rate of its execretion. In normal individuals this coefficient is held to be very constant but if the kidney function is impaired there is likely to be a relative increase in the concentration of urea in the blood and a relative decrease in its rate of excretion in the urine.

Ambard's first law is thus stated:

"If a constancy of the urea concentration in the urine is maintained, the square root of the urea eliminated in the urine in a definite interval is closely proportional to the concentrations of the urea in the blood." As variations in the concentration of urea in the urine alter the relationship of this to the urea concentration in the blood, Ambard formulated a second law to define the effect of this factor. His second law is: "If the blood urea remains at a constant concentration, the rate of urea excretion is inversely

proportional to the square root of the urea concentration in the urine."

The rate of elimination of urea also varies with the body weight, and is constant per kilogram of body weight, if other conditions are constant.

Ambard's formula is as follows:

$$K = \frac{U_R}{\sqrt{D\frac{20}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}}$$

K —coefficient of urea excretion.
Ur —urea grams per litre excretion.
D —urea grams in urine in twenty-four hours.
C —urea grams per litre of urine.
P —body weight in kilograms.
70 —standard body weight in kilograms.
25 —standard concentration of urea grams per litre of urine.

The normal coefficient averages 0·080 and varies between 0·050 and 0·090. Deficiency in urea excretion results in higher values and this higher value is due to the changed ratio between urea concentration in the blood and the excretion by the kidney.

McLean[25] modified this formula by designating the ideal normal rate of excretion as 100 and his index in a given case then expresses "in direct percentage the rate of excretion found, in terms of the rate of excretion that a normal individual would develop under the same conditions as to the concentration in the blood, concentration in the urine, and body weight."

$$\text{Index of excretion} = \frac{D\sqrt{C} \times 8.96\ (\text{CONSTANT})}{\text{Wt.} \times U_{R_2}}$$

D —grams urea excreted in twenty-four hours.
C —grams urea per litre of urine.
Ur —grams urea per litre of blood.
Wt —weight of body in kilograms.

The rate is not determined for twenty-four hours but for seventy-two minutes (i.e., $\frac{1}{20}$ of 24 hours).

The exact place these indices will assume in diagnosis and prognosis is by no means certain since very wide variations and discrepancies have been pointed out in individuals apparently in perfect health, by Addis and Watanabe.[26] Myers and Fine, as well as Jonas and Austin,[27] also criticize this method and claim the estimation of blood urea alone is more accurate, especially since slight carelessness in the collection of the urinary samples may very seriously affect the ultimate reading.

Mosenthal[28] has recently endeavoured to correlate some of the different tests of renal function and to indicate this approximately by + to + + + +, corresponding to slight, moderate, marked and maximal. I append his chart.

SCALE OF DEGREE OF IMPAIRMENT OF RENAL FUNCTION

Degree	Phthalein %	N.P.N. Blood mg. per 100 c.c.	Urea N. of Blood mg. per 100 c.c.	Ambard	Test Meal: Night urine c.c.	Night urine s.g.	Variations in S. G. when highest S. G. is: 18	17 to 15	14 to 13	12
Normal.....	60+	30 -	15 -	0.090	400 -	18+	9+			
+ slight.....	59–40	31–45	16–27	0.0910 to 0.115	400–600	16 & 17	8 to 5	6		
++ moderate.	39–25	46–65	28–44	0.116 to 0.220	600+	15 -	4 -	5 & 4	6+	
+++ marked.	24–11	66–90	45–64	0.221 to 0.350	...	....	....	3 -	4 & 5	6+
++++ max..	10–0	91+	65+	0.351+	...	....	....	....	3 -	5 -

There is still another aspect of nephritis which is deserving of reference in view of recent methods of investigation. I refer to the subject of acidosis,[30] which quite apart from nephritis, has attracted so much attention of late, and especially in the cases of recurrent vomiting in children, which is looked upon as due to this condition. May I refer briefly to the underlying principles.

Normal metabolic processes require a circulating medium of very constant reaction. Normal blood reaction, like normal temperature, is one of the important physiological constants. This "reaction" of the blood is faintly alkaline, or its hydrogen-ion concentration is only slightly less than that of pure water. To L. J. Henderson[29] we owe our conception of this fact.

By hydrogen-ion concentration we mean that a solution is acid when it contains an excess of hydrogen over hydroxyl ions; neutral when hydrogen and hydroxyl ions are in equal numbers and alkaline when the hydroxyl ions predominate. In solution through the influence of the solvent (water) acids, bases, and salts, dissociate or ionize, and each ionized molecule becomes resolved into its positive and negative ions, and these are known as cations (+) and anions (—) carrying a positive and negative electrical charge respectively. The extent to which acids and bases ionize, since all do not ionize to the same extent, determines their strength as such. The application of this fact shall appear shortly.

Since cellular activity demands such a constant reaction, there must be some delicate regulatory mechanism which will rapidly respond to even very slight variations in the reaction and set in operation some process by means of which the normal reaction of the blood is restored. This sensitive mechanism is possessed by the respiratory centre. Pulmonary ventilation is increased over 100 per cent. by an increase in the hydrogen-ion concentration of the blood which is smaller than any known laboratory method may detect.

During metabolic activity there are added to the blood stream certain acid products, which are a volatile acid CO_2 excreted by the lungs and non-volatile acids, or "fixed acids" excreted normally by the kidneys. The normality of the blood reaction is maintained by the chemical composition of the blood and the excretion of these acid substances.

The chemical composition of the blood assists in this process owing to the large amount of weak acids and their salts which it contains, e.g. carbonic acid, phosphoric acid, sodium carbonate, sodium bicarbonate, monosodium phosphate, and disodium phosphate. Then in addition there are the proteins of both basic and acid properties. Indeed the balance of weak acids and salts is such as to allow the addition of the maximum amount of acid with the minimum change of reaction of the blood.

The above mentioned salts and alkali protein compounds constitute the alkali reserve of the plasma and any diminution of this alkaline reserve is known as acidosis, and is recognized by clinical symptoms, changes in the blood and alveolar air.

The chief acid product of normal metabolism is CO_2. A slight increase in its presence stimulates the respiratory centre causing added pulmonary ventilation and a return to normal with no depletion of the alkali reserve or "buffer" substances as Hender-

son named them. If, however, a non-volatile acid such as sulphuric, phosphoric, or betaoxybutyric acid is poured into the plasma some of this alkali reserve is used up and the reaction or hydrogen-ion concentration shifts toward acidity. This stimulates respiratory ventilation which being unable to remove non-volatile acids removes more CO_2 than normal to compensate for the increase in non-volatile acids which it is unable to remove, resulting in a lowered CO_2 content of the blood in the lungs, and hence of the alveolar air in contact with this blood, through the lung membrane. Then this blood with its diminished alkali reserve comes in contact with the tissues once more and receives the CO_2 normally produced, the change in the blood toward acidity is more marked and overstimulation of the respiratory centre again results. The body endeavours to replenish the alkali reserve by production of ammonia and by the selective excretion of acid by the kidneys, retaining the bases in the body to neutralize more acids. If, however, more acids continue to be poured into the plasma and the alkaline reserve is depleted in spite of all safeguards, the alkalinity becomes less and less and a point is reached which is incompatible with life and this point is practically neutrality.

Now as is evident from dyspnœa, many advanced cases of nephritis develop an acidosis, not so much due to the excessive formation of acids as in diabetes mellitus, but to the impairment of their normal elimination by the kidney. As an index of this condition the CO_2 tension of alveolar air was measured, since the CO_2 tension of alveolar air is the same as that of aerated blood leaving the lungs for the tissues. Another method was to test the hydrogen-ion concentration of the blood. However, recently Van Slyke[31] has introduced a fairly simple method of estimation of the CO_2 combining power of the plasma and several investigators have found this CO_2 combining power to be moderately to markedly reduced in diabetes and nephritis.

Now in closing I may say that the amount of blood required to do all of the tests for retention which I have indicated is not large—about forty cubic centimeters. It is easily secured and keeps very well on ice, and is not necessarily absolutely sterile.

My remarks have extended over more time than I had at first anticipated and there are some tests for the estimation of renal function to which I have not referred at all. Those I have not mentioned are not looked upon by our best trained investigators and clinicians as contributing much of value to our knowledge of this most fascinating subject of renal pathological chemistry.

Some of these tests may seem of too theoretical value to be of vital interest to the busy physician or surgeon, but one has merely to recall that the theoretical procedure of to-day is often the daily routine of to-morrow. A few years ago "acidosis" was a term seldom heard apart from diabetes and terminal nephritis, while now acetone bodies are commonly demonstrated in the urine of children quite apart from either of the above diseases.

But to the busy practising physician and surgeon may I commend the estimation, in all your patients with albuminuria, or high blood pressure, or œdema, of the two-hourly urine characteristics, while on some improvised series of test meals along the lines I have indicated. Accurately measure the quantity and specific gravity of both day and night urines, and watch for nocturnal polyuria with lowered specific gravity as an initial sign of impending trouble.

To this test add the phenolsulphonephthalein which is simply applied, and the colorimetric reading readily made on an apparatus available now for a few dollars. Adding this information to careful clinical observation you shall have obtained a very fair estimate indeed of the condition of that wonderful organ, the kidney.

I have purposely refrained from any attempt at classification of kidney disorders beyond the very rough one of interstitial and parenchymatous. An exceedingly interesting grouping of Volhard and Fahr promises to go far toward classifying more adequately than ever before the known clinical and pathological data of nephritis.

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